REMARKS

Claims 1-18 are presently pending in the instant Application. In the instant Amendment, Applicants have amended Claims 2-10 merely to provide them with a more appropriate format, have canceled Claims 11-18, without prejudice, and have added new Claims 19-30. Support for amended Claims 2-10 as well as new Claims 19-30 can be found generally throughout the instant Application, and particular on page 6, lines 9-12; page 7, and in Claims 1-18 as originally filed.

The Invention is Unobvious

Claims 1-7 and 9 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,314,506 (the '506 patent). The Examiner has asserted that the '506 patent teaches the use of jets to create impinging fluid jet streams and thereby achieve high intensity micromixing of the fluids prior to nucleation in a crystallization process (column 4, lines 57-60). The Examiner also believes that the '506 patent teaches it is preferred that the two jet streams are substantially diametrically opposed to each other (col. 4, lines 63-65), and that the two fluids used can be of different solvent composition, one fluid being a solution of the compound to be crystallized in a suitable solvent or combination of solvents (feed solution), and the other being a suitable solvent or combination of solvents capable of initiating that compound's precipitation from solution (anti-solvent). The Examiner has also asserted that such solvents and anti-solvents can include, but are not limited to methanol, ethyl acetate, methylene chloride, acetonitrile, acetic acid, hexanes, ethers and water (col. 5, lines 7-20). In addition, the Examiner contends that the '506 patent teaches the use of much greater amounts of anti-solvent as compared with the solution comprising the medicament. With respect to the velocity of the streams used in the '506 patent, the Examiner has admitted that the '506 patent does not teach the velocity of the streams exceeds 30 m/s or 50 m/s. However, the Examiner has asserted that the '506 patent suggests that

a higher velocity is desirable, and that any limits on the upper limit of the velocity are only due to practical difficulties. The Examiner believes this teaching clearly suggests the use of velocities higher than 25 m/s. In light of the Examiner's interpretations of the teachings of the '506 patent, it is the Examiner's opinion that the '506 patent suggests the limitations of the instantly pending Claims, and that the process disclosed in the '506 patent achieves the same purpose as the instant invention, i.e. small particles with high surface area and high bioavailability, without the need for milling. Thus, it is the position of the Examiner that Applicants' Invention was *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made because the teachings of the '506 patent would motivate one of ordinary skill in the art to use as high a velocity as practically as possible, and the expected result would be a successful pharmaceutical formulation, as disclosed in the '506 patent.

Applicants respectfully traverse this rejection. Significant differences exist between the teachings of the '506 patent and the instant Invention that clearly would not be obvious to one of ordinary skill in the art in light of the teachings of the '506 patent alone, or in combination with other references the Examiner has cited. For example, the instant Invention clearly teaches that the ratio of the volume flow of anti-solvent to volume flow of medicament solution exceeds 2:1. Indeed, it is made clear at page 8, lines 10-13 of the instant Application that:

> As described above an excess of anti-solvent is needed and the ratio of the flow rate of anti-solvent to medicament solution must be greater than 2:1, preferably greater than 10:1, and even more preferably 15:1 and 30:1.

The Examiner has cited the examples of the '506 patent to support the assertion that the '506 patent teaches that much greater amounts of anti-solvent are used as compared to the amount of medicament solution used (paper No. 10, page 3). Yet, taken as a whole, the '506 patent contains no such teaching. In particular, example 2 of the '506 patent teaches "the flow

rate from ***each*** jet was 1.1 liter/min (emphasis added)." Similarly, Examples 6 and 7 of the '506 patent teach the volume flow rate for the anti-solvent and medicament solution are equal (see col. 6, lines 9-29 and lines 43-65, respectively). Example 5 even teaches the use of a ***greater*** volume of feed solution than anti-solvent (see col. 9, lines 60-67). Claim 16 of the '506 patent does teach the use of a volumetric ratio of 41:59 for feed solution to anti-solvent in a process for crystallizing simvastatin, which is greater than 1 (but hardly 2:1). Yet, col. 8, lines 9-14 of the '506 patent clarify:

> .... In this case, the composition of the impinging jet streams is 50:50 MeOH:H_2O, and the composition in the age tank is brought to 41:59 MeOH:H_2O by a separate, additional water injection ***(not through the impinging jet)*** directly into the stirred vessel (emphasis added)....

Furthermore, col. 67, lines 5-58 through to col. 7, lines 1-2 of the '506 patent make clear that, "....For example, if a 4:1 volumetric ratio of ***feed solution to anti-solvent*** is desired, the entry tube delivering solution should be twice the diameter of the entry tube delivering anti-solvent (emphasis added)."

In light of wide range of volumetric ratios used, the '506 patent, as a whole, clearly ***does not*** teach or suggest that the volume ratio of anti-solvent to medicament solution always be 2:1 or greater during the impingement of the jet streams. As one of ordinary skill in the art can readily see, in some instances, the '506 patent teaches that volume of anti-solvent present must be greater than the volume of feed solution present. Yet in other instances, it teaches that the volume ratio be 1:1, and in other instances, even teaches that that the volume ratio be ***less than 1***. Moreover, the '506 patent teaches excess of anti-solvent be added to the stirred vessel ***after*** the jets of medicament solution and anti-solvent have impinged upon each. Such teachings are in stark contrast to the teachings of the instant Application, i.e., that the volumetric ratio of anti-

solvent to medicament solution is at least 2:1, and all the anti-solvent used is delivered via the anti-solvent jet stream. Hence, taken as a whole, the '506 patent does not teach or suggest the instant Invention, ***and even teaches away from it.*** MPEP § 2141.02 makes clear that

> [a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)."

(Emphasis original).

Another significant and unobvious difference between the instant Invention and the teachings of the '506 patent was not even discussed or considered by the Examiner, i.e., that controlling the velocity of the jet streams to remove substantially cyclic variations results in a substantially higher quality of crystal. This aspect of the instant Invention is clearly recited in pending Claim 1. Support for this aspect can readily be found on page 5, lines 6-12 of the instant Application, wherein Applicants explain:

> Any variation in velocity of either or both streams can cause a variation in [particle size distribution] psd....It has also been observed that cyclic variations in either or both streams can lead to higher levels of residual solvent becoming entrapped in the crystal structure of the precipitated product.

On page 10 of the instant Application, Applicants provide data that clearly shows controlling the velocity of the streams to substantially remove cyclic variations clearly produce a higher quality crystalline product.

However, the '506 patent teaches or suggests ***nothing*** with respect to controlling the jet streams to remove substantially cyclic variations in stream velocity. Thus, for all of the foregoing Claim 1, currently Amended Claims 2-7 and 9, and new Claims 19-30 are clearly not obvious in light of the teachings of the '506 patent, and should be allowed to issue.

In addition, Claim 8 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over the '506 patent in view of the teachings of U.S. Patent 4,599,294 (the '294 patent). The Examiner's interpretations of the teachings of the '506 patent are discussed above. The Examiner has admitted though that the '506 patent does not specifically teach the use of the dimethylformamide as a solvent. However, the Examiner believes that the '506 patent teaches that the list of solvents disclosed therein and discussed above is not exhaustive. Hence, the Examiner is of the opinion that the DMF is a known solvent in the pharmaceutical art. In support of this opinion, the Examiner has relied upon the teachings at col. 10, lines 42-57 of the '294 patent, where a large list of solvents is found, including solvents such as DMF, methylene Chloride, and ethyl acetate. It is the position of the Examiner that one of ordinary skill in the art would have been motivated to use any known solvent in the teachings of the '506 patent to achieve the desired purpose, particularly because of the statement in the '506 patent that the list of solvents set forth therein is not exhaustive. Moreover, the Examiner believes the selection of a material based upon its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to the Applicant's specific selection. Hence, it is the Examiner's position that the instant Invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made.

Applicants respectfully traverse this rejection. Claim 8 is dependent upon Claim 1. Thus, all the elements of Claim 1 are incorporated into Claim 8. For reasons set forth above, Claim 1 is clearly not obvious to one of ordinary skill in the art with respect to the teachings of the '506 patent. Consequently, dependent Claim 8 is also not obvious, regardless of which solvent is used.

Moreover, contrary to the Examiner's assertion, a skilled artisan would not be motivated to combine the teachings of the '506 patent with the teachings of the '294 patent. As explained above, the '506 patent teaches, *inter alia*, a process for the crystallization of an organic pharmaceutical compound by contacting one or more jet streams of a feed solution of the organic pharmaceutical compound with one or more jet stream of an anti-solvent. In stark contrast, the '294 patent discloses, *inter alia*, a method of producing ***a dry spherical toner for printing***, wherein the method utilizes ***electrostatic force*** (see claim 1 of the '294 patent). MPEP § 2141.02 clearly teaches that in order for the Examiner to rely on a reference under 35 U.S.C. § 103, the reference must be ***analogous*** prior art. The Court of Appeals for the Federal Circuit has also explained, "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443,1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Since the teachings of the '294 patent clearly are not in the field of the instant Invention and the '506 patent (circular toner as opposed to a therapeutic agent), and are not reasonably pertinent to the particular problems with which both the '506 patent and the instant Invention are concerned, it is respectfully submitted that the '294 patent is directed to non-analogous art, and can not be relied upon in making this rejection. Thus, for all of the foregoing reasons, this rejection is obviated.

In addition, Claim 10 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over the '506 patent in view of the teachings of U.S. Patent 3,897,779 (the '779 patent). The Examiner's interpretations of the teachings of the '506 patent are discussed above. The Examiner has admitted though that the '506 patent does not teach the use of the active agent

triamcinolone acetonitride. However, the Examiner believes the '506 patent teaches that many active agents can be used. With respect to the '779 patent, the Examiner has asserted this patent teaches that triamcinolone acetonide is used in inhalation therapy, where high surface area, small particles, and improved stability and purity are greatly desired. Hence, it is the Examiner's opinion that triamcinolone acetonide would be an excellent medicament for the invention disclosed in the '506 patent. Moreover, the Examiner believes that, absent a showing of unexpected results, the use of a particular active agent in a known process does not impart patentability. Hence, in the opinion of the Examiner, the instant Invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made.

Applicants respectfully traverse this rejection. Claim 10 is dependent upon Claim 1, which for reasons set forth above is unobvious in light of the teachings of the '506 patent. The '779 patent teaches a method of treating asthma which "...is based on the discovery that the discharge from an aerosol container having therein a suspension of triamcinolone acetonide in a propellant can be suspended in a dry vaporized propellant mixed with air by the use of a deceleration chamber...." (Col. 1, lines 22-26 of the '779 patent). Since the '779 teaches ***nothing*** with respect to crystallizing a therapeutic compound, then Claim 10 is also unobvious with respect to the combination of the teachings of the '779 and '506 patents, and this rejection should be withdrawn.

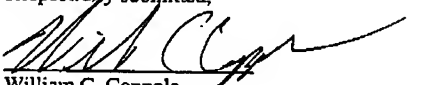
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



William C. Coppola
Registration No. 41,686

AVENTIS PHRAMACEUTICALS INC.
Route 202-206; Mail Code: D-303A
P.O. Box 6800
Bridgewater, NJ 08807